REVIEW

The challenge of mastitis

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The process of lactation and feeding, referred to by some as the final stage of labour is remarkably successful. This phase of infant care has been subjected to considerable evolutionary pressure since the earliest mammals, reptiles and birds diversified. It has allowed thousands of species to occupy a vast range of ecological niches. Yet a significant complication of breast feeding remains inflammation of the lactating tissue: the pathology of mastitis. Mastitis rarely develops outside lactation, although it may affect individuals at any age in relation to congenital lesions such as duct ectasia, chronic disseminated infections such as tuberculosis, or during granulomatous, autoimmune or malignant processes. The immunology and consequences of mastitis as well as its impact on vertical transmission of infection require careful examination.

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Mastitis in the lactating mother is important for paediatricians for two main reasons. Firstly, it is a major cause of reduction in milk production and approximately a quarter of mothers cite mastitis as their reason for stopping breast feeding.[1] Secondly, by altering the cellular composition of milk and local defences within the breast itself, mastitis is a powerful risk factor promoting vertical transmission of infections.[2] The condition may go on to give rise to a local abscess.

The diagnosis of mastitis is usually clinical, based on breast tenderness, signs of local inflammation, and a reduction in milk output. Parallels tend to be drawn with various domesticated animals, in which by contrast diagnosis rests on quantitative measures, the most common of which is an increased milk cell count.[3] Estimates of this are widely employed to assess agricultural milk quality with lower counts attracting higher milk prices. Other objective methods have included estimates of electrical conductivity and measures of specific enzymes or inflammatory mediators within milk (table 1).[4]

EPIDEMIOLOGY

Mastitis is relatively common, developing in 5–33% of women at some point during lactation.[1][5] Differences in case definition and reporting make accurate figures difficult to collect. The problem most commonly develops in the early stages of feeding, with 74–95% of cases observed in the first three months. It is usually unilateral. Rarely mastitis may develop at weaning. Breast abscess shows a similar epidemiological pattern and is found in 0.4–0.5% of lactating mothers. Abscess is rare after the first six weeks of lactation. Some mothers may suffer from recurrent mastitis, both with one infant and in successive pregnancies. Figure 1 outlines risk factors predisposing to mastitis as derived from clinical and veterinary studies. It is particularly interesting to observe that, despite the role of immunoglobulin in mucosal defences, relative deficiencies in IgA and IgG do not appear to predispose mothers or vetinary animals to mastitis in the developed world, although this may not be true in developing countries.[6–8]

Tradition and texts hold that mastitis is most frequently caused by stasis of milk, without significant deviation in "normal", "healthy" bacterial numbers or species. Milk stasis alone is a powerful stimulus to breast engorgement and the development of maternal fever. This condition was well described in wet nurses dependent on

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Table 1 Milk: changes in mastitis
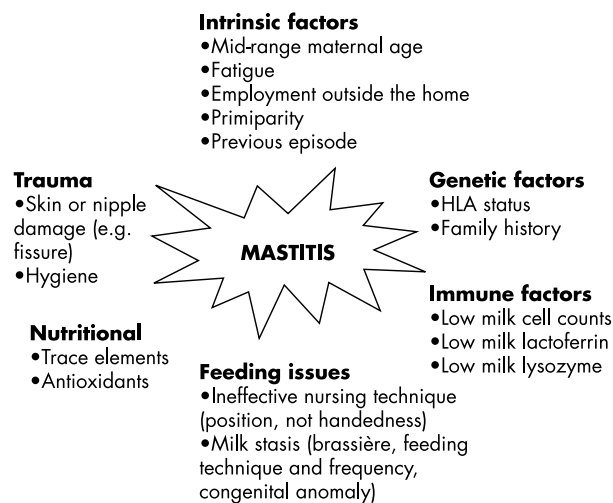
Biochemical	Increased sodium concentration Increased protein level
Cellular	Increased neutrophil count Activation of milk leucocytes
Proinflammatory mediators	Increased TNF-α and IFN-γ Increased RANTES, MIF
Counter-inflammatory mediators	Increased soluble TNF-α RII, IL-1ra
Endocrine	Decreases in triiodothyronine
Others	Increased electrical conductivity Altered mass spectrometry Alterations in enzyme content

TNF, tumour necrosis factor; IL, interleukin; IFN, interferon; IL-1ra, interleukin 1 receptor antagonist; MIF, macrophage inhibitory factor.

Intrinsic factors
•Mid-range maternal age
•Fatigue
•Employment outside the home
•Primiparity
•Previous episode

Trauma
•Skin or nipple damage (e.g. fissure)
•Hygiene

MASTITIS

Genetic factors
•HLA status
•Family history

Immune factors
•Low milk cell counts
•Low milk lactoferrin
•Low milk lysozyme

Nutritional
•Trace elements
•Antioxidants

Feeding issues
•Ineffective nursing technique (position, not handedness)
•Milk stasis (brassière, feeding technique and frequency, congenital anomaly)

Figure 1 Factors contributing to the development of mastitis.

regular suckling from their charges, and in the mothers who gave their babies to them. In different societies various cultural practices have developed to prevent stasis, such as the use of massage or herbal applications to promote expression of milk before and after birth.

On some occasions however, infection of the milk is readily detectable as bacterial colony counts increase and a small number of bacterial clones predominates. The most common organisms cultured are *Staphylococcus aureus*, followed by *Streptococcus* spp., Gram negative bacilli such as *Escherichia coli*, or mixtures of organisms. *Salmonella* spp., mycobacteria, candida, and cryptococcus have all been identified in rare instances. *S aureus* is responsible for the majority of hospital acquired epidemics of puerperal mastitis.[9] These organisms frequently colonise mothers, making the relative infrequency of infection striking, although few direct data are available on this subject. In a longitudinal study conducted for over a year in breast fed infants, Lindberg *et al* identified toxin producing staphylococcal species on maternal skin and in infant faeces, showing long term colonisation, without obvious clinical effect on mothers or infants.[10]

SUBCLINICAL MASTITIS
In subclinical mastitis there is no breast tenderness, but there is a reduction in milk output.[11] Human studies have shown biochemical changes in milk, and in domestic animals there is evidence of increased bacterial counts.[7] Subclinical mastitis leads to changes in the tight junctions between luminal epithelial cells, with a consequent leak of sodium, inflammatory cells, and other mediators into milk. Normal breast milk contains 5–6 mmol sodium; this increases to 12–20 mmol in subclinical mastitis. Raised levels of milk sodium are also seen in colostrum, at weaning, or in milk following preterm delivery. However, biochemical abnormalities have been observed in some women who are lactating normally, and have no breast pain. Subclinical mastitis is thought to be unilateral in the majority of women, and as with clinical mastitis, its prevalence is reduced by the provision of active counselling and advice to promote milk expression.[12] The natural history and clinical importance of subclinical mastitis remains unclear.

A SPECTRUM OF INFECTION?
Why does milk stasis produce inflammation? This question has no clear answer. Perhaps milk is a pro-inflammatory fluid—one might cite its content of proinflammatory substances including chemokines (such as RANTES), or macrophage inhibitory factor (MIF).[13] [14] Furthermore, most of the

cellular elements of milk (with the exception of its monocytes and macrophages) are in an activated state. Milk contains a range of proteins not found elsewhere in the body, and perhaps stasis promotes a situation in which there is a local adverse immune response to milk proteins. Stasis could even promote inflammation if milk were unstable, becoming more inflammatory if left in contact with breast epithelium for too long.

Milk itself is not sterile, and samples are inevitably colonised by those organisms found on the mother's skin. There is therefore no clear distinction between changes observed with stasis from those observed in subclinical mastitis or bacterial infection. It is probable that there is a spectrum of pathology in which mild changes initiated by stasis may be exacerbated by bacterial activity. One could propose a continuum from subclinical mastitis, to mastitis extending to breast abscess. The health of a lactating mother on this continuum would depend on the balance between host and organisms which themselves range from colonisers or commensals to infectious agents. Figure 1 outlines host factors involved in establishing this balance.

IMMUNOLOGY OF BREAST MILK
It is important to ask why evolution has not managed to sort out the problem of mastitis, or alternatively what mechanisms exist to prevent it developing. Although contemporary environmental factors such as the frequency of feeds, the wearing of a tight brassière, or maternal hygiene might increase this problem in man, these have not necessarily been relevant throughout evolutionary history. Immune components of milk have altered considerably in different mammalian phyla. Thus the amount of IgA varies dramatically, as do levels of most cytokines and mediators, even when corrected for protein level or fat content. Constant features of milks include the cellular content, in particular the granulocytes and monocytes. It is probable that cell recruitment from the maternal circulation therefore forms a central protective mechanism for breast secretions against infection. Further, it has been observed in dairy herds that those bred for the lowest milk cell counts are at highest risk of contracting mastitis. The roles of milk cells in protecting breast tissue and milk against contamination have received little attention in man, although in cows there is ample evidence that milk and the mammary gland are capable of independent phagocytosis, antigen presentation, and antibody secretion.[15] Might this proinflammatory profile be of evolutionary advantage by protecting against infection, or encouraging specific probiotics in the infant bowel?[16]

Curiously most monocytes in milk contrast with those in the maternal circulation in that they cannot be activated to become dendritic cells.[17] This limits their potential capacity to present antigen or drive T cell responses. Early observations suggested that this was because they were fat laden. Phenotyping suggests that it is rather due to a feature of cell recruitment. With mastitis this pattern changes and in mastitic milk activated dendritic cells may be identified.[18] These pose a more serious infectious hazard to the infant, as they may more readily carry virus particles. This Trojan horse problem has been illustrated in demonstrations that the types of HIV-1 virus spread by milk are not necessarily those one would expect to bind just to T lymphocytes.[19]

Mastitis itself leads to raised milk cell counts, and eventually raised bacterial counts if infection becomes dominant.[8] [9] Many questions remain to be addressed in lactation which revolve around milk colonisation by bacteria. Are luminal cells involved in cross talk with microorganisms, as are enterocytes in the bowel? In this microenvironment what receptors are expressed or nutrients exchanged? What is the role of milk components, including trafficking cells in the proposed continuum? Consideration of the breast milk duct as a

Table 2 Viral infections potentially transmissible through human milk

Virus group	Individual virus	Risk of transmission
Retroviruses	HIV-1	High
	HIV-2	Low
	HTLV-1	Moderate
Herpes viruses	CMV	High
Paramyxoviruses	Measles virus	Moderate
Hepatitis viruses	Hepatitis B	Very low
	Hepatitis C	Very low

bacterially colonised epithelial surface may allow progress to be made in dealing with the many unanswered questions in mastitis and lactation.

RISK OF INCREASED VERTICAL TRANSMISSION INFECTION DURING MASTITIS

Breast milk has the potential to transmit a number of viral pathogens (table 2). Clinical mastitis and breast abscess increases the risk of viral transmission from mother to infant.[2] For retroviruses this has been estimated as increasing the risk 2–4 times.[20 21] Globally, 30–60% of mother to child transmission of HIV-1 is caused by breast feeding; rates for HTLV-1 and HIV-2 are lower, although breast feeding remains a significant route of transmission.[22] The reasons for this increased risk may vary between mothers, but the HIV-1 viral load of milk, whether measured as free virus or cell associated virus increases with inflammation. Thus normal milk viral loads of less than 1000 copies of HIV RNA per ml increase 10- or 20-fold in mastitis.[20] This may result in an infant ingesting over 7 million copies of HIV RNA daily: a significant challenge to the antiviral defences in breast milk. Such studies are not entirely straightforward. A mother with mastitis is more likely to provide alternative milk feeds for her infant. This process of mixed feeding promotes increased intestinal permeability and may therefore facilitate viral entry independently of factors in the breast milk at the time.[23] Furthermore, the role of free virus or cell bound virus in such infections is not as clear as one might predict on the basis of increased breast milk viral copies.[24]

Existing guidance from WHO, UNICEF, and UNAIDS recommends that in developing countries, where safe alternatives to breast feeding are not available, HIV positive women with mastitis should continue to use the unaffected breast.[1]

Expression of breast milk and local pasteurisation may be used to render milk safe. However subclinical mastitis also increases the transmission rate of HIV. Its diagnosis relies on milk analysis, and thus is impracticable at present without developing a significant support structure. Population based approaches to the prevention of these conditions are required to make a significant impact on the vertical transmission rate of retrovirus in developing countries.

PREVENTION AND MANAGEMENT

Mastitis and breast abscess are preventable in most situations, so that expectant management is of value.[1] Early exclusive breast feeding, ensuring unrestricted access of the infant to the breast, together with support to establish and encourage exclusive demand breast feeds will reduce the risk of stasis. Correct positioning of the infant leading to proper attachment is likely to significantly reduce the majority of potential cases. Counselling and directed coaching of mothers has been shown to reduce subclinical mastitis too.

Should such measures fail, it is important to continue feeding from both breasts.[1] There is a role for the use of analgesics (preferably non-steroidal anti-inflammatory agents) and appropriate antibiotics. This should preferably be preceded by the culture of milk organisms. A large literature on herbal and traditional therapies exists, but most treatments have not been compared or assessed prospectively. In the case of abscess, pain may preclude feeding from that side and surgery may be required in rare instances. These treatments should not preclude continued breast feeding, and mothers should be supported with this advice so as to encourage continued lactation.

Protection by vaccination would seem to be an optimal approach; there is over a century of experience with this strategy in domesticated animals, with variable success (table 3). Early vaccination trials, including two series of pregnant mothers vaccinated with a staphylococcal toxoid, showed little benefit.[25] Efforts using bacterial interference in the USA, which employed a relatively benign strain of *S aureus* (502A) to colonise mothers and infants, met with some practical problems and was abandoned.[26] Similar work in Scotland with *S epidermidis* were similarly unsuccessful (Professor John Forfar, personal communication). Recent success with a human staphylococcal vaccine, based on a capsular polysaccharide conjugated with pseudomonas toxin suggests that those at risk of recurrent mastitis may be protected.[27]

THE FUTURE

Mastitis needs to be actively prevented; paediatricians can assist with this process. Further large prospective studies of lactation are needed. In order to increase the proportion of

Table 3 Experimental vaccines and immunotherapies

Immunotherapy strategy	Outcome
Alpha toxoid vaccines in ewes[28]	Protection against staphylococcal haemorrhagic mastitis
Panton Valentine leucocidin vaccine for pregnant mothers[25]	No clear benefit
Bacterial interference using *Staphylococcus aureus* 502[26]	No clear benefit
Streptococcal uberis vaccine 2002 in cattle[3]	Good short term protection
E coli J7 vaccine in cattle[3]	Good short term protection
Future vaccine targets	Staphylococcal polysaccharides
	Bacterial matrix binding proteins
	Biofilm or clumping molecules
	Modified superantigens/toxins

mothers providing exclusive breast feeding, more robust data are required to underpin accurate advice. Such studies will uncover important new aspects of milk biology, and the relative significance of mother's defences against those organisms which readily colonise milk and infant. New measurement methods, such as electrical conductivity or cytokine dipstick technologies, may assist with this. The development of vaccines against human commensals is advancing rapidly; this may open new avenues for the reduction of vertical transmission of serious viral infections and enhance the safety of breast feeding.

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